Considered /Wu-Cheng Winston Shen/ 01/08/2010

Docket No.:09857/0202272-US0
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Toshiyoshi Fujiwara et al.

Application No.: 10/520,901 Confirmation No.: 2780

Filed: April 13, 2005 Art Unit: 1632

For: ONCOLYTIC VIRUS REPLICATING SELECTIVELY IN TUMOR CELLS Examiner: W. C. W. Shen

DECLARATION OF TOSHIYOSHI FUJIWARA, UNDER 37 C.F.R. § 1.132

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, TOSHIYOSHI FUJIWARA, do hereby declare and state as follows:

1. I am a citizen of JAPAN and I am more than 21 years of age.

2. I graduated from Okayama University in 1985 with a degree in M.D. I also received a Ph.D. from Okayama University Graduate School of Medicine & Dentistry in 1990. A copy of my Curriculum Vitae is attached as **Exhibit 1**.

3. I make this Declaration in support of the above-identified application of which I am a co-inventor.

4. I have read and am familiar with the instant application as it was filed in the U.S. Patent and Trademark Office (USPTO), the pending claims, and the outstanding Office Action mailed on August 4, 2009 in connection with this application.

Presented herein are results of a clinical trial using the viral vector construct OBP-301, an adenoviral vector containing: hTERT promoter-E1A-IRES-E1B construct (as recited in claims 4 and 13). The methods utilized in the clinical trials also fall within the scope of the presently claimed methods for killing cancer cells (claims 8-11 and 17-20). The results of the clinical trials described herein further illustrate the ability of the claimed polynucleotide and vector constructs to replicate in cancer cells as well as to kill the cancer cells. This clinical trial was done under my supervision (*see* page 2, section 15 of INVESTIGATIONAL NEW DRUG APPLICATION (IND): **Exhibit 2**).

CLINICAL TRIAL

The following data provide additional details of data obtained from three patients out of a total of sixteen patients in the clinical trial described in the Declaration previously submitted on October 17, 2008.

Pt #01103
Investigator: Dr. John Nemunaitis, Mary Crowley Cancer Research Center, USA
Diagnosis: Metastatic Melanoma

In March of 2004, a 35 year old female, was diagnosed as advanced melanoma with metastasis to the liver and spleen. The patient was treated with temozolomide from May 2005-August 2005 with stable disease. She was also treated with interferon in July 2004 with stable disease. Recently, she was treated with an experimental dendritic cell vaccine, with overall response of PD. The baseline expression of hTERT mRNA in the biopsy tissue to be injected was positive.

On February 15, 2007, the patient received a single intratumoral injection of Telomelysin (1x 10^{10} VP) into the right breast mass (4.2 x 3.3 cm [13.9cm^2]).

On the next day after treatment, she experienced mild soreness at injection site, which was considered related to Telomelysin injection. And as the evidence of inflammation at the injected tumor, the peak of serum IFN-gamma and the peak of body temperature (37.1°C) were observed on day 1 after the injection.

On 28 days after injection, 27.3% tumor shrinkage was observed at treated tumor lesion (3.6 x2.8 cm [10.1cm^2]).

After the evaluation at the visit on day 28, the patient was subsequently enrolled into another clinical trial.

Pt# 01208
Investigator: Dr. John Nemunaitis, Mary Crowley Cancer Research Center, USA
Diagnosis: Metastatic Melanoma

On February of 2007, a 72 year old female with history of COPD, was diagnosed as melanoma at the left ankle. She received a knee amputation on April 5 of 2007 and a biopsy of the left inguinal node on the same day to find recurrence in the inguinal node. The recurred tumor was found at a left medial thigh node on May 11, 2007. She received 2 doses of interferon from June 11 to 18 of 2007. The baseline expression of hTERT mRNA in the biopsy tissue to be injected was positive.

On July 30 of 2007, the patient received a single intratumoral injection of Telomelysin (1x 10^{12} VP) into the tumor at medial left thigh (3.3 x 1.4cm [4.6cm^2]) of melanoma. She experienced mild bruising at the injection site and mild skin lesion from removing band-aid on day 7. As the evidence of inflammation at the injected tumor, the peak of IL-6 and IL-10 peak were observed on Day1. On the day 22, mild panic attack prior to visit. The panic attach was thought to be due

to information the patient heard about her brother. The patient contacted her physician's office and was instructed to take Xanax for her anxiety. The only adverse event thought to be probably related to study treatment was bruising at the injection site.

On day 28 after injection, 33.4% tumor shrinkage was observed at treated tumor lesion (2.8 x1.1 cm [3.1cm^2]), and pathological response were also observed at injected lesion. On day 56 after injection, 56.8% tumor shrinkage was observed at treated tumor lesion (2.5 x 0.8cm [2.0 cm^2]).

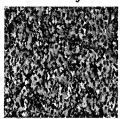
Day 0

CT Scan

x10 obj

A large part of the tissue is basophilic on Day 0

x40 obj

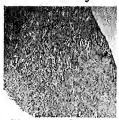


Infiltrative melanoma cells and lymphocyte infiltration

Day 28

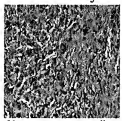
CT Scan

x10 obj



Tissues are rather eosinophilic on Day 28

x40 obj



No apparent tumor cells. Plasma cell infiltration.

Pt# 01214
Investigator: Dr. John Nemunaitis, Mary Crowley Cancer Research Center, USA
Diagnosis: Basal cell carcinoma

In 2001, a 54 year old male, was diagnosed as basal cell carcinoma in back. He had it removed surgically, and was diagnosed with basal cell cancer. One year later his disease recurred at the scar on his scalp. He then received a second surgery. Lung metastasis was found and followed by 2 cycles of Cisplatin and 5-FU in February 2005. The recurrence at scalp was found on

November 2007, and at the right neck and bilateral supraclavicular region, metastasis was found on December 6 of 2007. The baseline expression of hTERT mRNA in the biopsy tissue to be injected was positive.

On January 17 of 2008, he received a single intratumoral injection of Telomelysin ($1x\ 10^{12}$ VP) into the tumor at right suboccipital scalp (2.8 x 1.0 cm [$2.8cm^2$]). He experienced mild fever, achiness and chills on the day of study treatment. These adverse events were thought to be probably related to Telomelysin injection.

On day 28 after injection, 6.7% tumor shrinkage was observed at treated tumor lesion (1.7 x0.9 cm [$1.5cm^2$]). On day 56 after injection, the tumor size of treated tumor lesion remained the size as on 28 days after injection.

Conclusion

In the clinical trial, the viral vector construct OBP-301 according to the presently claimed vectors, was successfully and safely administered to the patients, and no serious side effects were observed. These results illustrate the targeting specificity of OBP-301 (i.e., the minimal, or few side effects indicate little or no replication in normal cells), and show the viral vector construct OBP-301 replicates in and specifically kills cancer cells.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 10/29/09

Toshiyoshi Fujiwara